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TELEFAX TRANSMITTAL

TO : Examiner Sharon L. Turner 1-703-308-0056 ✓
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FROM : Ian C. McLeod (517) 347-4100
DATE: 5/03/02 PAGES: 23 (including cover sheet)

Applicant : Alberto L. Mendoza
Serial No.: 09/082,112
Filed : 1998 May 20
For : METHOD AND VACCINE FOR TREATMENT OF
PYTHIOSIS INSIDIOSI IN HUMANS AND
LOWER ANIMALS
Docket No.: MSU 4.1-406

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Practitioner's Docket No. MSU 4-1-406

PATENT

#356
Enry
6/7/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Alberto L. Mendoza

Application No.: 0 9 /082,112 Group No.: 1647

Filed: 1998 May 20 Examiner: Sharon L. Turner, Ph.D.

For: METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN
HUMANS AND
LOWER
ANIMALS**RESPONSE UNDER
37 C.F.R. § 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP**

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GROUP 1600

Box AF

Assistant Commissioner for Patents
Washington, D.C. 20231

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AMENDMENT OR RESPONSE AFTER FINAL REJECTION—TRANSMITTAL

1. Transmitted herewith is an amendment after final rejection (37 C.F.R. § 1.116) for this application.

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*

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(Amendment or Response After Final Rejection—Transmittal (9-20)—page 1 of 4)

NOTE: Response to Final Rejection—Avoiding Extension Fees "In patent applications wherein a three month Shortened Statutory Period (SSP) is set for response to a Final Rejection, the response would best be filed within two months of the date of the Office Action. If filed within two months, any Advisory Action mailed after the SSP expires will reset the SSP to expire on the date of the Advisory Action for extension fee purposes, but never more than six months from the date of the Final Rejection." Notice of Nov. 30, 1990 (1122 O.G. 571 to 591). See M.P.E.P. § 714.13, 6th ed., rev. 3.

STATUS

2. Applicant is

- a small entity. A statement:
- is attached.
- was already filed.
- other than a small entity.

EXTENSION OF TERM

NOTE: As to a Supplemental Amendment filed in response to a final office action, the Notice of December 10, 1985 (1061 O.G. 34-35) states:

"If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run."

3. (complete (a) or (b), as applicable)

(a) Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. § 1.17(a)(1)-(4)) for the total number of months checked below:

Extension <u>(months)</u>	Fee for other than <u>small entity</u>	Fee for <u>small entity</u>
<input type="checkbox"/> one month	\$ 110.00	\$ 55.00
<input type="checkbox"/> two months	\$ 400.00	\$ 200.00
<input type="checkbox"/> three months	\$ 920.00	\$ 460.00
<input type="checkbox"/> four months	\$ 1,440.00	\$ 720.00

Fee: \$_____

If additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

An extension for _____ months has already been secured and the fee paid therefor of \$_____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request \$_____

OR

(b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. § 1.16(b)-(d)) has been calculated as shown below:

(Col. 1)	(Col. 2)	(Col. 3)	SMALL ENTITY	OTHER THAN A SMALL ENTITY
CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDIT. FEE OR RATE
TOTAL * 9	MINUS ** 20	= -0-	$\times \$9 =$	\$ -0-
INDEP. * 2	MINUS *** 3	= -0-	$= \$42 =$	\$ -0-
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			+ \$140 =	\$ -0-
			TOTAL \$	OR TOTAL \$
			ADDIT. FEE \$	-0-

- * If the entry in Col. 1 is less than entry in Col. 2, write "0" in Col. 3.
- ** If the "Highest No. Previously Paid for" IN THIS SPACE is less than 20, enter "20."
- *** If the "Highest No. Previously Paid for" IN THIS SPACE is less than 3, enter "3."
- The "Highest No. Previously Paid For" (Total or indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: See 37 C.F.R. § 1.116.

(complete (c) or (d), as applicable)

(c) No additional fee is required.

OR

(d) Total additional fee required is \$ _____

FEE PAYMENT

5. Attached is a check money order in the amount of \$ _____

Authorization is hereby made to charge the amount of \$ _____

to Deposit Account No. _____

to Credit card as shown on the attached credit card information authorization form PTO-2038.

WARNING: Credit card information should not be included on this form as it may become public.

Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.

A duplicate of this paper is attached.

(Amendment or Response After Final Rejection—Transmittal [9-20]—page 3 of 4)

FEE DEFICIENCY

NOTE: Where there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the case. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, (1065 O.G. 31-39).

6. If any additional extension and/or fee is required, charge Account No. 13-0610

AND/OR

If any additional fee for claims is required, charge Account No. 13-0610

Reg. No.: 20,931


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MSU 4.1-406
05/03/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alberto L. Mendoza

Serial No.: 09/082,112 Group Art Unit: 1647

Filed : 1998 May 20

For : METHOD AND VACCINE FOR TREATMENT OF
PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER
ANIMALS

Examiner : Sharon L. Turner, Ph.D.

Assistant Commissioner For Patents

Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. § 1.116(c)

Dear Sir:

In response to the Office Action mailed February 11, 2002, the applicant amends and remarks as set forth below.

Please be advised 5-6-02

In the Claims:

Please cancel Claim 24.

Please amend Claims 16, 18, 19 and 24 as follows.

-16- (Fifth amended)

A method for treatment of Pythiosis in human patients having Pythiosis which comprises:

(a) providing a vaccine containing a mixture of mixed intracellular proteins and mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution, wherein the mixed intracellular proteins, which consist essentially of all soluble proteins removed from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of all soluble proteins removed from the culture medium for growing the *Pythium insidiosum*, are in water and the mixture has been dialyzed to remove low molecular weight components less than 10,000 MW; and

(b) vaccinating the patient with the vaccine.

-18- (Fifth amended)

A method for the treatment of Pythiosis in a mammal having Pythiosis which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of all soluble proteins removed from

disrupted cells of the *Pythium insidiosum* separated from
10 the culture medium; and

(2) mixed extracellular proteins, which consist essentially of all soluble proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*;
15 wherein the admixture in water has been dialyzed to remove low molecular weight components less than 10,000 MW to produce the vaccine; and

(b) vaccinating the mammal with the vaccine.

-19- (Fifth amended)

The method of Claim 18 wherein the admixture is produced by growing cells of the *Pythium insidiosum* in the culture medium, killing the cells, separating the killed cells from the culture medium by centrifugation 5 to produce a first supernatant to provide the mixed extracellular soluble proteins of (a) (2), disrupting the killed cells in sterile water to produce a mixture consisting of soluble mixed intracellular proteins and insoluble disrupted cells, removing the insoluble 10 disrupted cells from the sterile water containing the soluble mixed intracellular proteins by centrifugation and discarding the insoluble proteins to provide the mixed intracellular proteins of (a) (1) in a second supernatant, combining the first and second

15 supernatants, precipitating the proteins, resuspending the precipitated proteins in sterile water, and dialyzing the resuspended proteins in sterile water to remove the material less than 10,000 MW.

REMARKS

Claims 16-25 are pending. No claims have been allowed. In the present amendment Claim 24 has been cancelled and its subject matter incorporated into Claim 19. Therefore, Claims 16-23 and Claim 25 remain pending.

The Claims have been amended to include the suggestions offered by the Examiner.

1. Claims 19 and 24 were rejected under 35 U.S.C. § 112, second paragraph.

In particular, the phrase "removing the disrupted cells from the sterile water containing the mixed intracellular proteins to provide the mixed intracellular proteins of (a)(1) in a second supernatant" in Claim 19 was pointed out as being indefinite to the skilled artisan as to what is being removed or what steps are being performed. The applicant has amended Claims 19 and 24 to clarify what is being removed.

With respect to the above phrase in Claim 19, the phrase has been amended to recite "disrupting the killed cells in sterile water to produce a mixture consisting of soluble mixed intracellular proteins and insoluble disrupted cells, removing the insoluble disrupted cells from the sterile water containing the

soluble mixed intracellular proteins by centrifugation and discarding the insoluble proteins to provide the mixed intracellular proteins of (a)(1) in a second supernatant . . ." It is believed that the above phrase satisfies the requirements of 35 U.S.C. § 112, second paragraph, and is supported by the specification in Example 1 on page 7.

Claim 24 has been cancelled because the centrifugation step recited therein has been incorporated into Claim 19.

In light of the above, Claim 19 is believed to comply with 35 U.S.C. § 112, second paragraph. Reconsideration of the rejection is requested.

2. Claims 16-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mendoza et al. (1996), Mendoza et al. (1992a) (IDS: AI), Mendoza et al. (1992b) (IDS: AJ), Sigma Catalogue (1992), Amicon Catalogue (1993), and Mendoza abstract (1995).

Claims 16 and 18 have been amended to claim a method which uses a vaccine wherein the mixed intracellular proteins consist essentially of all the soluble intracellular proteins removed from disrupted cells and the soluble extracellular proteins.

The applicant does not believe that the prior art would have rendered the applicant's presently

claimed invention *prima facie* obvious. M.P.E.P. § 706.02(j) sets forth the criteria that must be shown to establish that a claimed invention is *prima facie* obvious in view of a combination of prior art references. To establish *prima facie* obviousness, it must be shown that (1) there is some suggestion or motivation, either in the prior art references or the general knowledge of one of ordinary skill in the art to combine the reference teachings, (2) there is a reasonable expectation of success if the teachings of the prior art references were combined, and (3) the combined prior art references must teach or suggest all of the claim limitations. It is particularly important to show that there is some reason why one of ordinary skill in the art, with no knowledge of the claimed invention, would have selected the particular prior art references and combined them to render the claimed invention obvious. The case law has repeatedly insisted on such a showing (See In re Sang Su Lee, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002), for a brief review of the case law).

In the present case, the prior art provides no suggestion or motivation to one of ordinary skill in the art to combine the prior art references to produce a vaccine like the applicant's with any expectation of success. Furthermore, even when the prior art

references are combined, the combined prior art references do not teach or suggest every element of the applicant's vaccine.

The applicant's presently claimed method uses a vaccine that contains all the soluble intracellular proteins and the extracellular proteins in a mixture wherein material less than 10,000 MW has been removed. The applicant's vaccine has therapeutic characteristics that are more effective than either the CMV (intracellular protein vaccine) or SCAV (extracellular protein vaccine) of the prior art. Even though the applicant's vaccine contains intracellular proteins, unlike the CMV, the applicant's vaccine does not cause a prominent inflammatory response at the site of inoculation. The applicant's vaccine is able to cure horses that have been chronically infected with *P. insidiosum* for greater than 60 days (Specification: page 8, lines 22-27) and to cure all horses that had acute cases of *P. insidiosum* (Specification: page 8, lines 32-33). Furthermore, the applicant also provides in Example 4, the remarkable ability of the claimed vaccine to cure a human who had been infected with *P. insidiosum* for over 60 days. None of the prior art even hints at that possibility.

Mendoza (1992a) teaches two methods for producing *Pythium insidiosum* vaccines, a cell-mass

vaccine (CMV), which contains both soluble and insoluble proteins, and a soluble concentrated antigen vaccine (SCAV) which contains solely extracellular proteins. Both vaccines were of limited value for treating horses infected greater than 0.5 months but less than 2 months, and neither vaccine was effective for treating horse that had been infected for more than 2 months. Importantly, Mendoza (1992a) teaches that the CMV vaccine is undesirable because it has a short shelf-life and it causes a prominent inflammatory response at the site of inoculation. Thus, in light of Mendoza (1992a) one of ordinary skill in the art would not have been motivated to make a vaccine containing solely soluble intracellular proteins.

Mendoza (1992b) teaches preparing a mixture of intracellular antigens from *P. insidiosum* for use in Western blots. The teaches disrupting the cells and then removing the disrupted cell debris by centrifugation to produce a supernatant containing the antigens. As a person of ordinary skill in the art knows, the only reason the disrupted cell debris was removed from the intracellular antigens was to prevent the disrupted cell debris from clogging up the gel well thereby preventing the intracellular antigens from entering the gel. Mendoza (1992b) does not suggest such a preparation has use in a vaccine. As far as one

skilled in the art would know, the composition of Mendoza (1992b) would still have a short shelf-life and produce a prominent inflammatory response at the site of inoculation. Thus, one of ordinary skill in the art in view of Mendoza (1992a) and Mendoza (1992b) would not have been motivated to make a vaccine containing soluble intracellular proteins.

Mendoza (1995) discloses an SCAV vaccine containing three immunodominant intracellular proteins and Mendoza (1996) discloses an SCAV vaccine containing "cytoplasmic antigens, including the 28K, 30K and 32K immunodominant proteins" Both vaccines were reported to be able to cure horses chronically infected with *P. insidiosum*. Both Mendoza (1995) and Mendoza (1996) teach that the preferred vaccine would consist of the SCAV and the three immunodominant proteins. Neither suggests to a person of ordinary skill in the art to make a vaccine that contained all the soluble intracellular proteins (but not the insoluble proteins) and the extracellular proteins. At best, one of ordinary skill in the art would most likely be motivated to make a vaccine consisting of the SCAV and the three immunodominant proteins. But that vaccine would not contain all of the soluble intracellular proteins. Because of Mendoza (1992a), one skilled in the art would not be motivated to make a vaccine that consisted of the

SCAV and the CMV. Even if one skilled in the art were motivated to make a vaccine that consisted of the SCAV and the CMV, the vaccine would contain the insoluble proteins which are excluded in the applicant's vaccine. In addition, unlike the applicant's vaccine, both vaccines made in view of the prior art would contain material less than 10,000 MW. Thus, neither vaccine made in view of the prior art would have all the elements of the applicant's claimed vaccine: only soluble intracellular proteins and extracellular proteins greater than 10,000 MW.

It would have been particularly unlikely that one skilled in the art would have made the applicant's vaccine because Mendoza (1992a) teaches the CMV is unstable and causes a prominent inflammatory reaction at the site of inoculation. Therefore, in light of that and Mendoza (1995) and Mendoza (1996), which teach combining the three immunodominant proteins to the SCAV, a person of ordinary skill in the art would not have been motivated to add all of the soluble intracellular proteins to the SCAV because in view of the prior art (Mendoza (1992a)), the skilled artisan would have been expected a vaccine with a short shelf-life and limited efficacy and which causes a prominent inflammatory reaction. Even though Mendoza (1992b) teaches a composition containing soluble intracellular proteins

but which further includes material less than 10,000 MW, there is nothing in Mendoza (1992b) or Mendoza (1992a) or Mendoza (1995) or Mendoza (1996) which would suggest that the Mendoza (1992b) composition would not have the attributes of the CMV which Mendoza (1992a) teaches is undesirable.

Even when the prior art is considered further in view of Sigma and Amicon, the applicant's vaccine is not rendered *prima facie* obvious. Neither would have rendered the applicant's vaccine *prima facie* obvious because neither suggests that using any of the products therein for preparing a vaccine against Pythiosis would produce a vaccine with the properties of the applicant's vaccine, i.e., the ability to cure chronically infected horses and humans without causing a prominent inflammatory response. Mendoza (1992a) teaches using an Amicon stir-cell fitted with a PM-10 filter (Sigma) to concentrate only the proteins in the SCAV. None of the prior art teaches using the Amicon stir cell fitted with the PM-10 filter to concentrate intracellular proteins or that the Amicon stir cell fitted with the PM-10 filter is used for removing material less than 10,000 MW. Even if the Amicon stir cell fitted with the PM-10 filter did remove some or all of the extracellular material less than 10,000 MW, combining the extracellular material concentrated with the Amicon stir

cell fitted with the PM-10 filter with the intracellular material of Mendoza (1992b) would produce a composition that contained intracellular material less than 10,000 MW. That composition would be distinguishable from the applicant's vaccine. There is simply nothing in the prior art that would suggest to one of ordinary skill in the art that combining the soluble intracellular proteins with the extracellular proteins and then removing material less than 10,000 MW would produce a vaccine with the ability to cure horses chronically infected with Pythiosis but which retained all the desirable properties of the SCAV, i.e., did not have the undesirable attributes of the CMV (Specification: page 9, lines 8-14). Nor is there anything in the prior art that would have suggested that such a vaccine could cure a human chronically infected with Pythiosis. Therefore, the prior art simply does not render *prima facie* obvious the applicant's vaccine.

The only way for one of ordinary skill in the art to go from an SCAV which contains the three immunodominant proteins (Mendoza (1995) and Mendoza (1996)) to the applicant's vaccine in light of the prior art which teaches that a vaccine containing all the intracellular antigens is undesirable (Mendoza (1992a)) is to improperly use the applicant's disclosure as prior art. Without the applicant's disclosure, there is no

other way one of ordinary skill in the art would expect that an efficacious vaccine could be made by combining extracellular antigens with all the soluble intracellular antigens and removing material less than 10,000 MW. Nothing in the prior art suggests that preparing a vaccine against Pythiosis in the manner taught by the applicant would remove the undesirable attributes of the CMV without affecting the properties of the SCAV and which produce a vaccine with the ability to cure chronically infected horses similar to a vaccine consisting of the SCAV and the three immunodominant proteins. Nothing in the prior art would have suggested that such a vaccine could cure a human chronically infected with Pythiosis. The knowledge that the CMV could be modified as taught by the applicant, combined with the SCAV, and then dialyzed to remove material less than 10,000 MW to produce a vaccine with the ability to cure chronically infected horses and humans could only be gleaned from the applicant's disclosure. Thus, the present rejection is based upon hindsight reasoning.

Therefore, in light of the above, Claims 16-23 and 25 are not *prima facie* obvious over the prior art. Reconsideration of the rejection is requested.

Claims 16, 18, and 19 have been amended to place the claims in proper form for allowance or for appeal. The amendments to the claims are based upon the

statements made in the last Office Action. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Notice of Allowance is requested.

Respectfully,



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Ser. No. 09/082,112

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 24 has been cancelled.

Claims 16, 18, and 19 have been amended as follows.

-16-(Fifth amended)

A method for treatment of Pythiosis in human patients having [the] Pythiosis which comprises:

(a) providing a vaccine containing a mixture of mixed intracellular proteins and mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution, wherein the mixed intracellular proteins, which consist essentially of all soluble proteins removed from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of all soluble proteins removed from the culture medium for growing the *Pythium insidiosum*, are in water and the mixture has been dialyzed to remove low molecular weight components less than 10,000 MW; and

(b) vaccinating the patient with the vaccine.

-18- (Fifth amended)

A method for the treatment of Pythiosis in a mammal having [the] Pythiosis which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of all soluble proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and

(2) mixed extracellular proteins, which consist essentially of all soluble proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*;

wherein the admixture in water has been dialyzed to remove low molecular weight components less than 10,000 MW to produce the vaccine; and

(b) vaccinating the mammal with the vaccine.

-19- (Fifth amended)

The method of Claim 18 wherein the [removed proteins in the] admixture [have been provided] is produced by growing cells of the *Pythium insidiosum* in the culture medium, [then] killing the cells, [then] separating the killed cells from the culture medium by

10 centrifugation to produce a first supernatant to provide the mixed extracellular soluble proteins of (a) (2) L [and then] disrupting the killed cells in sterile water to produce a mixture consisting of soluble mixed intracellular proteins and insoluble disrupted cells, [and] removing the insoluble disrupted cells from the sterile water containing the soluble mixed intracellular proteins by centrifugation and discarding the insoluble proteins to provide the mixed intracellular proteins of
15 (a) (1) in a second supernatant, combining the first and second supernatants, precipitating the proteins, resuspending the precipitated proteins in sterile water, and dialyzing the resuspended proteins in sterile water to remove the material less than 10,000 MW.